

# Treatment of Hyperemesis Gravidarum

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Hyperemesis gravidarum, or pernicious vomiting of pregnancy, is a complication of pregnancy that affects various areas of the woman's health, including homeostasis, electrolytes, and kidney function, and may have adverse fetal consequences. Recent research now provides additional guidelines for protection against and relief from hyperemesis gravidarum. Alterations to maternal diet and lifestyle can have protective effects. Medicinal methods of prevention and treatment include nutritional supplements and alternative methods, such as hypnosis and acupuncture, as well as pharmacotherapy.

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## KEY WORDS

Hyperemesis gravidarum • Nausea • Vomiting • Pregnancy

**H**yperemesis gravidarum, or pernicious vomiting of pregnancy, is a complication of pregnancy that affects various areas of the woman's health, including homeostasis, electrolytes, and kidney function, and may have adverse fetal consequences. Nausea and vomiting are common in pregnancy, affecting up to 70% to 85% of pregnant women.<sup>1</sup> Hyperemesis affects between 0.3% and 2.3% of all pregnancies.<sup>2</sup> The condition is defined as uncontrolled vomiting requiring hospitalization, severe dehydration, muscle wasting, electrolyte imbalance, ketonuria, and weight loss of more than 5% of body weight.<sup>3</sup> Most of these patients also have

hyponatremia, hypokalemia, and a low serum urea level.<sup>4</sup> Ptyalism is also a typical symptom of hyperemesis.<sup>5</sup> The symptoms of this disorder usually peak at 9 weeks of gestation and subside by approximately 20 weeks of gestation.<sup>6</sup> Approximately 1% to 5% of patients with hyperemesis must be hospitalized.<sup>7</sup> Women who experienced hyperemesis in their first pregnancy have a high risk for recurrence.<sup>6,8,9</sup>

The differential diagnosis of hyperemesis gravidarum (Table 1) includes urinary tract infection, uremia, thyrotoxicosis, diabetic ketoacidosis, Addison disease, hypercalcemia, gastritis, peptic ulcer disease, pancreatitis, bowel obstruction, hepatitis,

**TABLE 1****Differential Diagnosis of Vomiting During Pregnancy**

Thyrototoxicosis
Diabetic ketoacidosis
Addison disease
Hypercalcemia
Gastritis
Gastroparesis
Peptic ulcer disease
Pancreatitis
Appendicitis
Acute fatty liver of pregnancy
Bowel obstruction
Hepatitis
Kidney stone
Urinary tract infection
Uremia
Drug-induced vomiting
Migraines
Central nervous system disease
Vestibular disease

drug-induced vomiting, central nervous system (CNS) disease, and vestibular disease.<sup>4,10</sup> It may also cause Mallory-Weiss tears and esophageal rupture.<sup>6,11</sup> If not appropriately treated, it may cause severe adverse effects, including neurologic disturbances, such as Wernicke encephalopathy, central pontine myelinolysis, and even maternal death.

Studies have focused on the reasons some pregnant mothers develop hyperemesis; however, the cause has not yet been clearly identified. The pathogenesis is not fully understood, but may be attributed to hormones, gastrointestinal (GI) dysfunction, thyrotoxicosis, serotonin, hepatic abnormalities, autonomic nervous dysfunction, nutritional deficiencies, asthma,<sup>8</sup> allergies,<sup>12</sup> *Helicobacter pylori* infection,<sup>13</sup> or psychosomatic causes.<sup>8,14</sup>

This condition does not just affect the mother. Babies born to mothers

battling hyperemesis have a variety of different obstacles to overcome before becoming healthy. The infants of mothers with hyperemesis may be born prematurely, be small

women with and without hyperemesis.<sup>16</sup> Neurological maturity was also not affected by age 1 year.

Hyperemesis has a tremendous detrimental effect on the weight of

*The infants of mothers with hyperemesis may be born prematurely, be small for gestational age, have significantly lower birth weights, or have 5-minute Apgar scores of < 7.*

for gestational age, have significantly lower birth weights,<sup>15</sup> or have 5-minute Apgar scores of < 7.<sup>8</sup>

In a meta-analysis completed by Veenendaal and colleagues,<sup>16</sup>

newborns, which is a focus of recent research. When comparing women with hyperemesis having < 7 kg of weight gain during pregnancy with women who gained  $\geq$  7 kg,

*When comparing women with hyperemesis having < 7 kg of weight gain during pregnancy with women who gained  $\geq$  7 kg, the risk of a small for gestational age infant was increased.*

pregnant women with hyperemesis gravidarum were more likely to deliver babies who were born small for gestational age (odds ratio [OR] 1.28; 95% confidence interval [CI], 1.02-1.60). Hyperemesis was also found to be associated with delivery before 37 weeks of gestation when compared with subjects without hyperemesis (OR 1.32; 95% CI, 1.04-1.68).<sup>16</sup> There may be an association between hyperemesis and testicular cancer, which may be due to hormonal imbalance. It has been reported that the increase of in-utero estradiol in women with hyperemesis gravidarum may prevent the infant's testes from descending.<sup>16</sup>

Although hyperemesis has clear detrimental effects, there are areas of study that show limitations in the ways in which infants can be affected. When comparing infants born at an early gestational age to those who were not, there was no significant difference in Apgar scores, congenital anomalies, or perinatal death.<sup>16</sup> In this study, there were no significant findings in long-term outcomes between

the risk of a small for gestational age infant was increased (OR 1.5; 95% CI, 1.0-2.2).<sup>16</sup> Also, babies of women with < 7 kg of weight gain had an increased risk of having a 5-minute Apgar score of < 7 (OR 5.0; 95% CI, 2.6-9.6) compared with babies from the control group.<sup>16</sup> The authors concluded that hyperemesis itself is not a risk factor for adverse outcomes, but these outcomes are the consequence of the low weight gain associated with hyperemesis. With minimal weight gain, adverse outcomes for the newborns have been noted.<sup>16</sup>

If a mother does have significant weight loss during pregnancy, it can create further complications. In a retrospective analysis, patients who had > 5% weight loss and were malnourished have experienced adverse pregnancy outcomes.<sup>16</sup> These results include low birth weight, antepartum hemorrhage, preterm delivery, and an association with fetal anomalies. There are reports of congenital malformations such as undescended testicles, hip dysplasia, and Down syndrome.<sup>16</sup> Studies also have shown an increased incidence of

CNS malformation. Researchers agree that the vomiting is most likely not teratogenic, but the untreated electrolyte disturbances, malnutrition, and maternal weight loss may be harmful.<sup>10</sup> Babies may experience severe effects as a result of the complications of maternal hyperemesis.

The effects of hyperemesis gravidarum are quite widespread. In addition to feeling ill, women with this condition report other sources of distress, including time lost from work and decreased quality of life.<sup>6</sup> In a study of 147 patients, 82.8% were restricted in their everyday activities. They reported being limited not only due to the nausea and vomiting, but also from the psychological affliction that was caused by feeling ill for weeks to months.<sup>6</sup> Women have also reported feeling treated differently socially as well as in the workplace. Hyperemesis can result in financial hardship for these patients, their places of employment, and the health care system,<sup>6</sup> showing that the effects of the disease are not limited to pregnant women alone.

Recent research now provides additional guidelines for protection against and relief from hyperemesis gravidarum. These treatment methods include a range of options, from routine changes to medications and various different therapies. Alterations to maternal diet and lifestyle can have protective effects. Medicinal methods of prevention and treatment include nutritional supplements as well as alternative methods, such as hypnosis and acupuncture.

### Diet

Modification of the amount and size of meals consumed throughout the day may help relieve symptoms. Having smaller amounts of

food and fluids more often can help prevent mild cases of nausea and vomiting from worsening. The meals should contain more carbohydrate than fat and acid.<sup>6</sup> Protein-rich meals also decrease symptoms. Lighter snacks, including nuts, dairy products, and beans, are often endorsed. Drinks that contain electrolytes and other supplements are advised. If certain foods or food preparations trigger nausea, they should be avoided.

### Lifestyle

Women who are affected by this illness should avoid stress and try to get as much rest as possible. If emotional support is needed, the patient can see a psychologist to help address the debilitating symptoms. Supportive counseling or crisis intervention may be necessary.<sup>6</sup>

### Intravenous Fluids

Intravenous (IV) fluids should be provided to replenish the lost intravascular volume. Rehydration along with replacement of electrolytes is very important in the treatment of hyperemesis. Normal saline or Hartmann solution are suitable solutions; potassium chloride can be added as needed. While replacing electrolytes, the physician must consider the risks of rapid infusion in order to prevent such conditions as central pontine myelinolysis.<sup>4</sup>

### Thiamine

Thiamine should be a routine supplement in patients with protracted

thiamine may be diluted in 100 mL of normal saline and infused for 30 minutes to 1 hour weekly.<sup>4</sup>

### Antiemetics

Several common drugs are used as antiemetics to control nausea and vomiting during pregnancy. They should not be used before 12 to 14 weeks of gestation due to possible detrimental effects to the developing fetus.<sup>4</sup> However, there are data showing lack of teratogenicity with the use of dopamine antagonists, phenothiazines, and histamine receptor blockers.<sup>4</sup>

In their 2004 guidelines on vomiting in pregnancy, the American Congress of Obstetricians and Gynecologists recommended that the first-line antiemetic medications be IV dimenhydrinate, metoclopramide, or promethazine.<sup>1</sup> In a double-blind study conducted by Tan and colleagues,<sup>2</sup> promethazine and metoclopramide were found to have similar therapeutic effects for the treatment of hyperemesis ( $P = .47$ ), but there were fewer adverse effects with metoclopramide.<sup>2</sup> Medications included promethazine, 25 mg, or metoclopramide, 10 mg, every 8 hours for 24 hours. Metoclopramide caused significantly less frequent drowsiness ( $P = .001$ ), dizziness ( $P < .001$ ), and dystonia ( $P = .02$ ) when compared with promethazine.<sup>2</sup>

In a study by Nageotte and colleagues,<sup>17</sup> patients using a combination treatment of droperidol and diphenhydramine had significantly shorter hospital stays for hyperemesis, fewer days hospitalized for hyperemesis during pregnancy,

*Thiamine should be a routine supplement in patients with protracted vomiting.*

vomiting. Pregnant women should ingest a total of 1.5 mg/d. If this cannot be taken orally, 100 mg of

and fewer readmissions for hyperemesis compared with those who were not treated with droperidol

or diphenhydramine as a primary therapy.<sup>17</sup> Droperidol was dosed initially at 1.0 to 2.5 mg, depending on severity of symptoms, and administered over 15 minutes. A continuous infusion was then started at 1.0 mg/h. If the symptoms persisted, the amount was increased to 1.25 mg/h, and increases from that point were made in 0.25-mg increments every 4 hours. Droperidol is structurally related to haloperidol; it did not cause abnormal fetal or neonatal outcomes, and there were no maternal adverse outcomes, including hypotension.<sup>17</sup>

Ondansetron is a 5-HT<sub>3</sub> antagonist that acts on the CNS and peripheral nervous system. The primary location of action is in the CNS, but it also increases gastric emptying. It is very effective for patients who experience the emetic effects of chemotherapy.<sup>18</sup> It also aids patients with postoperative nausea and vomiting. A study on ondansetron found it to decrease vomiting after the first dose and decrease nausea subsequently.<sup>18</sup> The patient studied was able to tolerate a light diet after 2 days of treatment, and she was discharged 14 days after being admitted on 4 mg of ondansetron three times daily.

## Steroids

The mechanism of action of steroids is assumed to be a direct effect on the vomiting center of the brain. Because such high doses are required, it is improbable that there is a lack of pituitary adrenal reserve in this illness.

One study showed vomiting ceased in all patients within

between 15 and 45 mg/d helped patients resume eating, reverse muscle wasting, and regain lost weight from prepregnancy weight. After discharge, maintenance doses of  $\geq 15$  mg/d were used from 6 to 20 weeks.<sup>5</sup> There is no clear evidence of steroid teratogenicity.<sup>5,15</sup> It is advised that steroids only be used after all other causes of vomiting have been excluded, vomiting has continued for more than 4 weeks and is associated with dehydration, and the risks and benefits of the treatment have been explained.<sup>5</sup>

In a randomized, double-blind, controlled study comparing steroids and promethazine for the treatment of hyperemesis, steroids were found to be more effective.<sup>19</sup> Oral methylprednisolone, 16 mg, was administered three times daily, and promethazine, 25 mg, was administered three times daily. No women were readmitted to the hospital who were treated with methylprednisolone, but five patients from the promethazine group were readmitted to the hospital for hyperemesis within 2 weeks of discharge. Neither drug displayed adverse effects.

## Ginger

The GI symptoms of motion sickness and hyperemesis are similar; therefore, the root of ginger, *Zingiber officinale*, has been studied to treat hyperemesis. The effectiveness of ginger is thought to be dependent on its aromatic, carminative, and absorbent characteristics. It is thought to act on the GI tract to increase motility, and its absorbent property may decrease stimuli to the chemoreceptor zone

responses and consequent nausea feedback.

In a double-blind, randomized, crossover trial, 1 g of ginger was administered daily for 4 days. The preference among the patients to receive ginger versus placebo was significant.<sup>12</sup> Concurrently, the relief of nausea and vomiting found with the use of ginger compared with placebo was significantly greater. In a study by Vutyavanich and associates,<sup>20</sup> 1 g of ginger was given to women with hyperemesis for 4 days, and two measuring scales were implemented to quantify patients' nausea.<sup>20</sup> The improvement in the nausea scores of patients receiving ginger was significantly greater than that of the placebo group. Also, after 4 days of treatment, there was a significant decrease in vomiting in the ginger-treated group versus the placebo-treated group.<sup>20</sup> However, different collections of ginger may differ due to their growing climates, conditions, and harvesting times.<sup>20</sup> There have been no teratogenic effects of ginger in this or other studies.<sup>12</sup>

## Nasogastric Enteral Feeding

In one study of seven patients with hyperemesis, the placement of a Dobhoff tube improved symptoms of nausea and vomiting in 24 hours, and symptoms continued to improve with enteral feedings. The mean hospitalization after feedings began was 4.6 days, with the longest being 8 days. On discharge, one woman did not require enteral feedings, and the other six continued feedings in the outpatient setting. The average duration of feedings was 43 days, ranging from 5 to 174 days. One patient was content with the enteral feedings and continued them for 174 days; however, the second longest duration was only 49 days.<sup>21</sup>

*One study showed vomiting ceased in all patients within 3 hours after administration of the first dose of IV hydrocortisone.*

3 hours after administration of the first dose of IV hydrocortisone. Maintenance doses ranging

in the medulla that sends stimuli to the emetic center of the brain stem. Ginger may also block the GI

This treatment has potential complications, such as pneumothorax aspiration, infection, venous thrombosis, intrahepatic cholestasis, and fatty infiltration of the placenta. In order to minimize the possibility of aspiration, the feeding tube was placed past the pylorus. This technique, however, exposes the patient to radiation to check the position of the tube. Despite its expense, it is considerably cheaper compared with total parenteral nutrition (TPN). This type of feeding is most useful in patients whose nausea and vomiting are associated with the consumption of food.<sup>21</sup>

### Total Parenteral Nutrition

TPN is a nutrient source that may be used in pregnant women who suffer from severe hyperemesis or

were defined by indirect calorimetry, and the appropriate number of calories was calculated for each patient. The group of hyperemesis patients compared with the two control groups of healthy pregnant women and healthy women who were not pregnant had significantly different substrate utilization. The hyperemesis patients used fat, consistent with a catabolic state. The hyperemesis group also had a mean respiratory quotient that was  $< 1.00$ , an indication of a catabolic state. After treatment with TPN, the respiratory quotient of each hyperemesis patient was  $> 1.00$ , showing a shift to utilization of carbohydrate and protein, indicating an anabolic state and improvement in nutritional status. The pre- and posttreatment mean respiratory quotients of the hyperemesis group

should begin at 30 to 45 mL/h and increase in increments of 20 mL/h/d.<sup>3</sup>

Fat emulsions have been shown to induce contractions of the uterine muscle at a high infusion rate.<sup>3,22</sup> This may happen at any point in the pregnancy. Placental infarctions and placental fat deposits are also a risk with fat emulsion infusions, possibly resulting in placental insufficiency.<sup>3,22</sup> Fat emulsions should not exceed 3 g/kg/d, or more than 60% of the total calories, to avoid a fat overload.<sup>22</sup> TPN should be discontinued once the woman is able to tolerate enteral feedings.<sup>22</sup> Infections are also a risk of TPN, and vigilant observation must be practiced.<sup>4</sup> More severe risks when using TPN include sepsis and cardiac complications due to electrolyte imbalances.<sup>1</sup>

*TPN is a nutrient source that may be used in pregnant women who suffer from severe hyperemesis or when there is a lack of absorption of adequate nutrients.*

when there is a lack of absorption of adequate nutrients.<sup>22</sup> The severe nutritional deprivation caused by hyperemesis is preferably treated with enteral hyperalimentation, but if the patient cannot tolerate this and vomits after feeding, the risk of aspiration increases. TPN has been used in other conditions to sustain pregnancies, such as jejunoleal bypass, diabetes, and Crohn disease.<sup>3,22</sup> TPN is a nonprotein calorie source, usually glucose or lipid emulsions, that provides utilizable nitrogen, electrolytes, trace elements, water, and fat-soluble vitamins. This source of calories prevents ketosis, which develops from fatty acid metabolism and may have adverse effects on the fetus.

In order to study the nutritional effects of hyperemesis, the basal metabolic expenditure and adjusted metabolic expenditure

were significantly different. The birth weights of the infants surpassed the average birth weights for their respective gestational ages.<sup>3</sup>

Complications of the TPN catheter include pneumothorax, puncture of nearby artery, or air embolism.<sup>22</sup> There are also risks when using TPN due to the infusion of such a large amount of glucose. The consequences are similar to a woman with diabetes during pregnancy. Hyperglycemia may cause fetal anomalies and complications. Elevations in the mother's glucose may increase the risk of having a macrosomic baby.<sup>3,12</sup> An infusion with a high amount of glucose may compromise respiration if carbon dioxide is overproduced.<sup>22</sup> Hypertonic dextrose infusions should be started slowly at 40 mL/h or 1 L/d, then increased.<sup>3</sup> If administering solutions containing 25% or more of dextrose, the infusion

### Acupuncture

In addition to standard treatment, acupuncture to PC6, which is the point 5 cm proximal to the wrist crease on the palmar side of the forearm, could quicken the resolution of hyperemesis. In a placebo-controlled, randomized, single-blind, crossover study, acupuncture treatments were given for 30 minutes three times a day because, in previous studies, an 8-hour treatment effect had been shown. Women in the active acupuncture group versus the placebo group had a significantly quicker decrease in the amount of nausea they experienced.<sup>14</sup> There was also a significant difference in the amount of vomiting between the two test groups. The active acupuncture group had significantly fewer patients vomiting. There was no significant difference in food intake between the two groups, and no side effects were observed.

There are a few possible mechanisms of action for the reduction of

hyperemesis from acupuncture. It seems to inhibit nociceptive transmission and autonomic reflexes. It also seems to decrease pain in the system from the periaqueductal gray, which partially works through endorphinergic mechanisms. Because one potential cause of hyperemesis is reduced gastric emptying, and acupuncture has an effect on the GI tract, another possible mechanism of action is through somatovisceral reflexes.<sup>14</sup>

### Hypnosis

Hypnosis is used to control physiologic changes that are thought to be involuntary. Hypnotized patients have, however, been able to control sympathetic tone, vasoconstriction, and vasodilation, heart rate, and muscle tone.<sup>7</sup> It has been compared with biofeedback because patients are trained to voluntarily control these mechanisms. Biofeedback uses an external method of feedback whereas hypnosis uses an internal control from the patient.

Hypnosis works through a dissociation of content, when the individual's attention is focused on a certain task causing the rest of the information surrounding him or her to be temporarily unreachable. An example of this is the unnoticed hum of a computer motor.<sup>7</sup> Hypnosis also acts through dissociation of context, in which this narrowing of attention briefly suspends higher-order processes.<sup>7</sup>

In the case examples of hypnosis treating hyperemesis performed by Simon and Schwartz,<sup>7</sup> the treatment was found to be effective in two ways. The first component is a deep relaxation that acts to decrease sympathetic nervous system arousal.<sup>7</sup> This decreases the sympathetic hyperaroused state. The second component is the response to hypnotic suggestion of symptom removal. This response to suggestion is independent of the sympathetic or parasympathetic systems and is often independent of their conscious awareness or memory of

the suggestion.<sup>7</sup> It is, however, necessary to dispel any myths or doubt the patients have about hypnotic treatment. No teratogenic effects were noted.<sup>7</sup> It is also proposed that expanding this treatment to women with morning sickness would prevent the nausea and vomiting from worsening or progressing to hyperemesis gravidarum.

### Conclusions

Nausea and vomiting are positive predictors of a favorable pregnancy outcome, but excessive vomiting may have negative effects on the mother and baby, including low birth weight, antepartum hemorrhage, preterm delivery, and failure of infant testes to descend. In order to alleviate this nausea and vomiting, the simplest changes are to eat more frequent, smaller meals and avoid foods or odors that trigger vomiting. Another lifestyle alteration is to decrease stress and get more rest throughout the day. Thiamine should be supplemented

**TABLE 2**

**Summary of Treatment Agents**

Agent	Dosage	Efficacy	Safety
Metoclopramide	10 mg every 8 h for 24 h	Reduces nausea and vomiting	Less drowsiness, dizziness, dystonia No known malformations
Promethazine	25 mg every 8 h for 24 h	Reduces nausea and vomiting	No known malformations
Diphenhydramine	12.5-25 mg every 4-6 h	Reduces nausea and vomiting	No increased risk of malformations Causes drowsiness
Droperidol and diphenhydramine	1.0-2.5 mg over 15 min, then 1.0 mg/h	Reduces nausea and vomiting	No abnormal outcomes
Ondansetron	50 mg over 30 min every 6 h 4 mg every 8 h	Reduces nausea and vomiting after first dose	
Methylprednisolone	16 mg every 8 h		No known malformations
Ginger	1 mg for 4 d	Reduces nausea and vomiting	No known malformations

at 1.5 mg/d in women with hyperemesis. When these methods do not help, IV fluids should be administered to replace the lost fluid and electrolytes.

The medications found to improve hyperemesis gravidarum symptoms without causing detrimental effects to the fetus are listed in Table 2. Metoclopramide, when compared with promethazine, proved to cause less drowsiness, dizziness, and dystonia. Steroids were found to relieve symptoms better than promethazine, but are only to be used if all other causes of vomiting have been excluded. Ginger was found to significantly improve the nausea and vomiting of hyperemesis. With severe hyperemesis, more invasive measures have been shown to improve symptoms. Nasogastric feedings relieved symptoms and decreased length of hospital stay. TPN shifted the patients from a catabolic state to an anabolic state and improved their nutritional status. This method, however, does have risks.

Alternative treatment with acupuncture resulted in significantly less vomiting. The use of acupuncture plus administration of IV fluids improved symptoms faster than placebo plus IV fluids.

Although the exact mechanism of action is unknown, there are no known adverse effects on the baby. By entering a deeply relaxed state and decreasing the sympathetic state through hypnosis, women with hyperemesis have reported improvement in their nausea and vomiting.

Hyperemesis gravidarum is a potentially severe condition that can cause detrimental changes in the pregnant woman and her fetus. In order to decrease these effects, managing the nausea and vomiting as well as their consequences, will prevent harmful or undesired outcomes. The current medications and treatments reviewed here will aid in proper management and relief of this disorder. ■

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### MAIN POINTS

- Hyperemesis gravidarum, or pernicious vomiting of pregnancy, is a complication of pregnancy that affects various areas of the woman's health, including homeostasis, electrolytes, and kidney function, and may also have adverse fetal consequences. The pathogenesis is not fully understood, but may be attributed to hormones, gastrointestinal dysfunction, thyrotoxicosis, serotonin, hepatic abnormalities, autonomic nervous dysfunction, nutritional deficiencies, asthma, allergies, *Helicobacter pylori* infection, or psychosomatic causes.
- Hyperemesis itself is not a risk factor for adverse outcomes, but these outcomes are the consequence of the low weight gain associated with hyperemesis. Patients who had > 5% weight loss and were malnourished have experienced adverse pregnancy outcomes, such as low birth weight, antepartum hemorrhage, preterm delivery, and an association with fetal anomalies.
- Treatment methods include a range of options, including maternal diet and lifestyle alterations, administration of intravenous fluids, antiemetics or steroids, and alternative therapies such as acupuncture and hypnosis.